Studies on the role of mesolimbic dopamine in behavioural responses to chronic nicotine.

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There is good evidence that nicotine can evoke the secretion of dopamine (DA) in the mesolimbic system of the brain and that this effect mediates the psychostimulant response to the drug and its ability to act as a reward in self-administration schedules (1,4). This presentation will summarise the results of three experiments we have performed to characterise the effects of chronic nicotine on DA secretion in the mesolimbic system and the behavioural consequences of the changes observed.

In the first series of experiments microdialysis studies were performed in freely moving rats, which had been pretreated with daily injections of saline or nicotine (0.4 mg/kg SC for 5 days), using probes located in the nucleus accumbens. On the day of the experiment the animals were left in activity boxes for 2h before being given an injection of saline or nicotine (0.4 mg/kg SC). Under these conditions both acute and subchronic nicotine increased ($P<0.01$) locomotor activity and increased the concentration of dihydroxyphenylacetic acid (DOPAC) in the dialsysate ($P<0.05$). Subchronic, but not acute, nicotine increased ($P<0.01$) the concentrations of DA and homovanillic acid (HVA) in the dialysate. The increase in locomotor activity evoked by subchronic nicotine was also greater ($P<0.05$) than that observed for rats treated acutely with the drug. In a second series of experiments the mesolimbic DA system was lesioned by injecting 6-hydroxydopamine bilaterally into the nuclei accumbens. In agreement with previous studies (1,2), the lesion suppressed the locomotor responses to nicotine (0.1 or 0.4 mg/kg SC) ($P<0.01$) and d-amphetamine (0.5 mg/kg SC) ($P<0.001$) whereas pretreatment with nicotine (0.4 mg/kg daily for 7 days) enhanced the responses to nicotine ($P<0.001$) but not amphetamine. The lesion also suppressed ($P<0.05$) the activity of rats both pretreated and tested with saline but not the activity of rats tested with saline after pretreatment with nicotine (0.4 mg/kg SC). In a third study rats treated with saline, nicotine (0.4 mg/kg SC) or d-amphetamine (0.5 mg/kg SC) were trained on a shock avoidance schedule using the procedure described Morrison (3). In agreement with the previous study, nicotine-withdrawal from rats trained with nicotine caused a significant disruption ($P<0.05$) of avoidance performance. The withdrawal of d-amphetamine from rats trained with d-amphetamine also disrupted avoidance performance ($P<0.01$) whereas its administration to nicotine-withdrawn rats attenuated the effect of withdrawal.

In summary, the results of the three studies taken together provide evidence for the hypothesis that chronic treatment with nicotine may enhance its effects on DA secretion in the mesolimbic system and that this effect of the drug may be associated both with the enhanced locomotor responses observed in rats treated chronically with the drug and the development of nicotine dependence.

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